REMARKS

Interview Summary

Pursuant to 37 CFR §1.133(b), Applicants acknowledge with appreciation the in-person interview with the Examiner on December 8, 2005 during which the following outstanding issues were discussed. In particular, Applicants discussed the claim rejections under 35 U.S.C. §112, first paragraph, regarding enablement and written description.

Applicants agreed to submit arguments and supporting publications concerning the predictability of generating multiple antibodies that share the same binding specificity based on a common CDR3 sequence in the relevant technology of recombinant fully human antibodies, as well as the predictability and lack of undue experimentation involved with making conservative sequence modifications within the CDR domains that do not affect antibody binding.

Information Disclosure Statements

The Examiner notes that certain references cited in the IDSs previously filed in the present application have not been received. Accordingly, Applicants have resubmitted herewith the 1449 or SB-08 forms for each of the three IDSs previously submitted and their accompanying references as Appendix A. Applicants respectfully request the Examiner to consider the enclosed references and initial the 1449/SB-08 forms accordingly. In addition, Applicants submit herewith a supplemental IDS for the Examiner's consideration.

Pending Claims

Claims 1, 2, 5-11, 15, 17-22, 29-33, 35, 36 and 56-62 were pending in the application and have been canceled. New claims 94-107 have been added. Support for new claims 94-107 can be found throughout the specification as originally filed.

For example, support for isolated human antibodies, or antigen binding portion thereof, that bind to human dendritic cells and comprise of at least a heavy chain CDR3 sequence, or conservative sequence modifications thereof, can be found at least at page 15, lines 27-33, and page 35, lines 19-26.

Support for isolated human monoclonal antibodies, or antigen binding portions thereof, that bind to human dendritic cells which comprise a full complement of CDR domains (*i.e.*, SEQ ID NOs:2 and 4, or conservative sequence modifications thereof) is found, *e.g.*, in original claim 51.

Support for new claims 100-107 can be found, *e.g.*, in original claims 31, 1, 8, 5 and page 3, lines 4-20.

The foregoing claim amendments should in no way be construed as acquiescence to any of the Examiner's rejections, and have been made solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed or as previously pending in this or in one or more separate applications. No new matter has been added.

Rejection of Original Claim 81 Under 35 U.S.C. §112, Second Paragraph

Original claim 81 is rejected "as being indefinite" based on its reference to human germline V_H5-51 and V_KL15 genes. According to the Examiner, such terms "comprise undefined laboratory designations."

Applicants respectfully traverse this rejection. However, to expedite prosecution, claim 81 has been canceled.

Rejection of Original Claims 79-91 Under 35 U.S.C. §112, First Paragraph

Original claims 79-91 are rejected as not being enabled. In particular, the Examiner maintains that the claims must recite the full framework sequences along with the full complement of CDR domains to be enabling. According to the Examiner, undue experimentation would be required to practice the invention as claimed because "little is known in the prior art about the nature of the invention and the art is unpredictable." Specifically, the Examiner states that:

> the specification must show that an antibody defined only by the 6 CDRs of SEQ ID NOs:2 and 4 would function for its intended use. In addition . . . [f]or the antibodies of the claims to function, *i.e.*, minimally, to bind their disclosed antigen, the antibody's CDRs would have to play a major role in antigen binding. While CDRs play a major role in antigen binding, it is well-established that they do not play an exclusive role in said binding. See, for example Potter *et al.* (2002) wherein the authors teach that amino acid residues within the framework region of an antibody can be critical for antigen binding (see particularly, Figure 2). Chien *et al.* (1989) teaches that even amino acids outside the framework region can be critical for antigen binding (see particularly, Figure 2). And Tempest *et al.* (1994) teaches that even when antigen binding and affinity are maintained, minor substitutions in the framework region of an antibody can grossly affect antibody activity (see particularly, Table 2 and Figure 2). Thus, the notion that all that is required to define an antibody are 6 CDR regions is firmly dispelled by the antibody engineering art.

Applicants respectfully traverse this rejection. As discussed below and evidenced by the enclosed pre-filing publications, the critical structural feature that confers the binding specificity of a recombinant antibody is the heavy chain CDR3 domain. Accordingly, based on the detailed teachings contained in the present specification, combined with the level of skill in the art at the time the application was filed, one of ordinary skill could have prepared without undue experimentation multiple human antibodies based on a common CDR3 sequence all having the same binding specificity and affinity. Indeed, as evidenced by the enclosed publications, it was predictable and well known how to utilize a given CDR3 sequence only to generate other recombinant antibodies having the same binding specificity and affinity, yet different CDR2, CDR1 and framework sequences. Thus, contrary to the Examiner's position, it is not necessary to define all six CDRs and the framework of a recombinant antibody, such as the presently claimed human antibodies, to enable the generation of multiple other antibodies having the same binding specificity.

It was well established that the CDR3 region alone could be used to generate antibodies having the same antigen specificity

As evidenced by the enclosed publications, it was well established in the art at the time of the present invention that the CDR3 domain alone can determine the specificity of an antibody and, importantly, that multiple antibodies can be predictably generated based on a common CDR3 sequence, without undue experimentation. Specifically, the following references provide evidence supporting these art recognized aspects of antibody architecture and binding, and the role of the CDR3 region in particular: Klimka *et al.* (2000) British J. of Cancer 83(2):252-260; Beiboer *et al.* (2000) J. Mol. Biol. 296:833-849; Rader *et al.* (1998) PNAS USA 95:8910-8915; Barbas *et al.* (1994) 116 J. Am. Chem. Soc. 2161-2162; Barbas *et al.* (1995) 92 PNAS USA 2529-2533; and Ditzel *et al.* (1996) 157 J. of Immunol. 739-749 (Appendices B, C, D, E, F and G, respectively).

Klimka *et al.* describe the production of a humanized anti-CD30 antibody using only the heavy chain variable CDR3 domain, *i.e.*, the major determinant for epitope-specificity, of a murine anti-CD30 antibody, Ki-4. The human version of the murine anti-CD30 antibody was produced by sequentially replacing the murine variable heavy and light chain genes with human V gene repertoires, while retaining only the heavy chain CDR3 domain of the murine Ki-4 antibody (see Abstract; page 253, column 1, second full paragraph; and page 255, "Results"

section, last paragraph of column 1-column 2). As demonstrated by Klimka *et al.*, the anti-CD30 antibody was found to compete with the parental murine antibody for binding and to retain other functional characteristics of the parental murine antibody (*e.g.*, inhibits the shedding of the extracellular part of the CD30 receptor from L540 cells).

With regard to the importance of the retained VH-CDR3 domain, Klimka *et al.* explicitly state that this region is known "for its significant importance in determining the binding specificity of an antibody" (page 259, left column, first full paragraph). The authors also conclude that "this region was important in retaining the CD30-epitope specificity of the parental antibody in the humanized scFv." Still further, the authors note that the "importance of the VH-CDR3 for epitope specificity has also recently been reported by Beiboer *et al.* (2000), thereby confirming our findings" (page 269, left column, first full paragraph).

Like Klimka *et al.*, Beiboer *et al.* generated recombinant antibodies using only the heavy chain CDR3 sequence of a parent antibody. Specifically, the authors engineering an antibody to epithelial glycoprotein-2 (EGP-2) by retaining only the murine heavy chain CDR3 domain of the murine MOC-31 antibody. As confirmed in Beiboer *et al.*, "the heavy chain CDR3 is the main loop involved in antigen binding . . . " (page 839, left column, last full paragraph). The newly created antibody was found to bind the same epitope and have a similar binding affinity as the parental murine antibody.

Similarly, using only the CDR3 sequence of a parent antibody, Rader *et al.* describe the production of a humanized anti-integrin $\alpha_v\beta_3$ antibody using the heavy and light chain variable CDR3 domains of the murine anti-integrin $\alpha_v\beta_3$ antibody, LM609. Rader *et al.* report that several antibodies were produced having different sequences outside the CDR3 regions and capable of binding the same epitope as the parent murine antibody with affinities as high or higher than the parent murine antibody.

Further evidence showing that functionally equivalent recombinant antibodies could indeed be generated without undue experimentation at the time of the present invention using only the CDR3 region of a parent antibody and, importantly, the predictability of generating multiple antibodies having the same binding specificity based on a common CDR3 sequence is provided by Barbas *et al.* (1994) who describe a method for generating antibodies having high affinity for double-stranded DNA. In particular, Barbas *et al.* successfully generated isolated antibodies by antigen selection from synthetic libraries which utilized the same heavy chain with

randomized CDR3 sequences. The authors concluded that the CDR3 provides the most significant contribution to antigen binding (page 2161, left column, second full paragraph).

Moreover, in a separate publication, Barbas *et al.* (1995) also describe grafting the heavy chain CDR3 sequences of three Fabs, SI-1, SI-40 and SI-32, against human placental DNA onto the heavy chain of an anti-tetanus toxoid Fab, thereby, replacing the existing heavy chain CDR3. The results of these studies showed that grafted Fabs produced binding to DNA (page 2532, second paragraph, and the Abstract) and, thus, that the CDR3 alone conferred binding specificity.

Similarly, Ditzel *et al.* also describe grafting studies which showed that a heavy chain CDR3 only can be transferred to the heavy chain of another antibody and retain the same binding specificity. Specifically, the heavy chain CDR3 sequence of the polyspecific Fab LNA3 was grafted onto the heavy chain of the monospecific IgG tetanus toxoid-binding Fab p313, thus, replacing the existing heavy chain CDR3 (paragraph bridging columns on page 740). The binding specificity of the LNA3 heavy chain CDR3-grafted Fab (LNA3/p313) was tested in an ELISA against a panel of exogenous and autoantigens (Figure 3). LNA3/p313 bound to the panel of antigens as did the original LNA3 Fab (page 742, second column, through page 744, first column and Figure 3e).

As evidenced by the foregoing publications, it was clearly established in the art at the time of the present invention that the heavy chain CDR3 alone is sufficient to define binding specificity of an antibody and that multiple antibodies can predictably be generated having the same binding specificity based on a common CDR3 sequence. The foregoing publications also evidence that, once provided with the CDR3 sequence of a given antibody, it was well within the ordinary skill of the art to have generated other antibodies having the same binding specificity. Accordingly, based on the knowledge, evidence, predictability and skill in the art at the time of the present invention, and the ample teachings in the present application with respect to, for example, how to generate fully human antibodies that bind to human dendritic cells, it is clear that the presently pending claims are fully enabled.

Conservative amino acid substitutions within CDRs that do not affect antibody binding were well within the skill of the art at the time of the invention

As amended, the presently pending claims encompass human antibodies which bind to human dendritic cells having particular CDR and variable region sequences and conservative

sequence modifications of these CDR sequences. As known in the art, "conservative sequence modifications" refer to modifications that do not substantially affect or alter the binding characteristics of the antibody containing the claimed amino acid sequence and include amino acids in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Such families of amino acid residues having similar side chains were well known in the art as evidenced by, for example, Stryer, *Biochemistry*, 2nd ed., Chapter 2, pages 13-15 (attached as Appendix H). Moreover, antibodies having such substitutions can be tested using routine immunoassays, *e.g.*, ELISA or flow cytometry (see the Examples section of the present application), for the antibody's ability to bind human dendritic cells without requiring undue experimentation by one of ordinary skill in the art. Therefore, the presently claimed antibody sequences and conservative sequence modification thereof are fully enabled.

Indeed, Applicants respectfully note that CDR domains are short sequences of only between 4 and 16 residues in length. Given this short length, combined with the knowledge and high level of skill in the antibody art at the time of the invention, one of ordinary skill in the art could have made, without undue experimentation, conservative sequence substitutions within, for example, the claimed CDR3 sequences without affecting antibody binding. Moreover, it was well known in the art that CDR and other variable region residues critical for binding could be identified by comparing the antibody heavy and light chain variable region sequences to their respective germline sequences to identify which residues were amenable to conservative modification and which were not, *i.e.*, which residues had been conserved and which had been somatically mutated to improve binding.

Accordingly, based on the substantial knowledge and high level of skill in the art at the time of the present invention, it would not have been unpredictable, or have required undue experimentation, to have generated antibodies which retain dendritic cell binding having conservative sequence modifications within the variable or CDR regions of the recited sequences as presently claimed.

The references relied on by the Examiner do not establish unpredictability with respect to generating fully human antibodies that bind to human dendritic cells having the CDR3 sequence presently claimed

The Examiner relies on three references in support of the position that functional human monoclonal antibodies could not have been predictably generated "by replacing the CDR regions

of an acceptor antibody with the CDRs of a donor antibody." The Examiner also relies on these references in support of the position that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformations are required in order to produce the fully human antibodies as claimed. Specifically, the Examiner points to Potter *et al.* (2002) to argue that "amino acid residues within the framework region of an antibody can be critical for antigen binding," as well as Chien *et al.* (1989) as teaching that "even amino acids outside the framework region can be critical for antigen binding." The Examiner further relies on Tempest *et al.* (1994) to argue that "even when antigen binding and affinity are maintained, minor substitutions in the framework region of an antibody can grossly affect antibody activity."

Applicants respectfully disagree and note that none of the references relied on by the Examiner relate to the production of fully human monoclonal antibodies, as presently claimed. Thus, these references do not speak to the predictability of the claimed invention.

Indeed, Tempest *et al.* describe CDR-grafted humanized antibodies of a monoclonal antibody (MAb78) against human tumor necrosis factor-α which retain the CDRs of the original mouse with or without a varying number of original framework residues and found that all versions of the humanized antibodies showed loss of binding affinity, except one. Unlike recombinant human antibodies, humanized antibodies include CDRs from a non-human antibody (*e.g.*, a mouse antibody) and a framework region from a human antibody. This requires modifications to the framework regions to maintain binding, because of the differences in antibody structure and incompatibilities between the species.

In contrast, in the case of fully human antibodies as presently claimed, CDRs are cloned into frameworks from the same species and, thus, are inherently more stable (*e.g.*, by virtue of naturally occurring CDR-framework interactions) than humanized antibodies. In addition, as a result to their greater stability, recombinant fully human antibodies are more amenable to amino acid sequence modifications, particularly conservative modifications which do not affect charge, compared to other recombinant antibodies, such as humanized antibodies.

Accordingly, in the art of generating recombinant antibodies based on CDR regions (*e.g.*, a given CDR3) from another (parent) antibody, the predictability of maintaining binding of the parent antibody is far greater in the field of fully human antibodies *versus* humanized antibodies. For at least this reason, the references relied on by the Examiner, which do not pertain to the recombinant expression of fully human antibodies, do not establish unpredictability with respect

to generating fully human antibodies that bind to human dendritic cells based on a common CDR3 sequence, as presently claimed.

The references of Potter *et al.* and Chien *et al.* also do not pertain to recombinant antibodies or provide evidence that it would have required undue experimentation to have generated human antibodies that bind to human dendritic cells as presently claimed. Indeed, these references merely show that certain residues within antibody variable regions are critical for binding, not that it would have required undue experimentation or have been outside the ordinary skill in the art at the time of the invention, to have identified such residues, particularly with respect to recombinant fully human antibodies. Indeed, it was well within the skill of the art to have identified such residues. Moreover, Chien *et al.* describe studies in which a non-conservative amino acid substitution (*e.g.*, substitution of asparagine with alanine) was made near the antigen binding pocket, as opposed to conservative substitutions as presently claimed.

Overall, the question whether certain amino acid modifications can affect binding of an antibody is not the relevant inquiry in the present case. The relevant inquiry is whether one of ordinary skill at the time of the present invention would have been able to make and use recombinant fully human antibodies which bind to human dendritic cells having at least the recited CDR3 sequence without undue experimentation. As discussed in detail above and evidenced by the enclosed supporting publications, the answer is clearly yes: that the claimed antibodies are fully enabled given the knowledge, high level of skill and predictability in the art at the time of the present invention, combined with the detailed teachings of Applicants' specification.

Rejection of Original Claims 79-91 Under 35 U.S.C. §112, First Paragraph

Original claims 79-91 are rejected under 35 U.S.C. §112, first paragraph, as being "new matter." The Examiner states that the specification and the claims as originally filed do not provide support for the antibodies as claimed.

(A) Original Claim 79

With regard to original claim 79, drawn to an isolated human antibody or portion thereof which binds to human dendritic cells comprising CDR domains having specific amino acid sequences, the Examiner states that " . . . the specification does not adequately describe antibodies comprising the claimed CDRs in other framework regions."

Applicants respectfully traverse this rejection. The written description requirement requires that the specification show possession of the claimed invention. As discussed above, based on the CDR sequences provided in the present claims and disclosed in the present application, one of ordinary skill in the art clearly had possession of other human antibodies having the same CDRs within different human frameworks.

Importantly, as recently articulated by the Federal Circuit, it is firmly established that the descriptive text needed to meet the Written Description requirement varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence. *Capon v. Eshhar*, 418 F.3d 1349, 1357 (Fed. Cir. 2005). In *Capon*, the Federal Circuit explained that "since the law is applied to each invention in view of the state of the relevant knowledge, its application will vary with differences in the state of knowledge in the field and differences in the predictability of the science." *Id.* Specifically, the Court stated that:

> Precedent illustrates that the determination of what is needed to support generic claims to biological subject matter ***depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter***. *Id.* at 1359 (emphasis added).

The Court further explained that "the written description may be satisfied 'if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure.'" *Id.* (citing *Amgen Inc. v. Hoechst Marion Roussel*, Inc., 314 F.3d 1313, 1332 (Fed. Cir. 2003). Accordingly, "[a]s each field evolves, the balance also evolves between what is known and what is added by each inventive contribution." *Id.* at 1358.

Accordingly, under current law, ***the standard for meeting the Written Description requirement differs for every patent specification*** depending upon a number of factors, including the scientific knowledge in existence at the time of the invention, the skill in the art, the predictability of the claimed subject matter, and correlation of a described function to a known structure. In some cases, describing an invention only in functional terms or by partial structure (*e.g.*, sequence) may suffice if this information demonstrates possession of the claimed invention in view of the state (*e.g.*, maturity, skill and predictability) of the art. In other cases, for example, where the art is nascent, a more complete description may be required to evidence possession of the claimed invention.

As previously discussed above in the context of enablement and further below, when considered in light of these factors, the present disclosure clearly meets the Written Description

requirement and demonstrates that Applicants were in possession of the claimed invention at the time of filing, and that the present claims do not encompass new matter. Importantly, the prior art clearly established that recombinant antibodies having the same binding specificity could be predictably generated based on a common CDR3 sequence, and also demonstrated that the science of generating such antibodies was highly mature.

Specifically, the enclosed supporting prior art publications clearly establish that, once provided with a CDR3 sequence of an antibody, one of ordinary skill in the art had possession of other recombinant antibodies having the same binding specificity with different CDR1, CDR2 and framework regions. Similarly, the enclosed publications also show that the science of generating recombinant antibodies having the same binding specificity with different CDR1, CDR2 and framework regions was highly mature at the time of the present invention. The enclosed publications further establish the predictability of generating human antibodies based on a common heavy chain CDR3 region. When evaluated in light of these significant factors, the descriptive text provided in the present disclosure clearly meets the written description requirement for the presently claimed invention.

For at least the foregoing reasons, Applicants respectfully request that the present rejection under 35 U.S.C. §112, first paragraph, be withdrawn.

(B) Original Claim 80

The Examiner states that the claimed antibodies, or antigen binding portions thereof, which include the variable heavy and light chain regions comprising SEQ ID NOs: 2 and 4, respectively, are not supported by the specification. The Examiner further states that the specification:

> does not disclose entire antibodies comprising these regions . . . Applicant has argued . . . that the specification and prior art would have allowed for the production of antibodies comprising these variable regions. Applicant is advised that such an argument would be appropriate for a rejection for lack of enablement; the instant rejection is for inadequate written description.

Applicants respectfully traverse this rejection and refer to the arguments set forth immediately above, the substance of which is reiterated here. In particular, as recently articulated by the Federal Circuit in *Capon v. Eshhar*, the standard for meeting the Written Description requirement depends upon a number of factors, including the scientific knowledge in existence at the time of the invention, the skill in the art, the predictability of the claimed

subject matter, and correlation of a described function to a known structure. Accordingly, these factors must be considered when evaluating whether Applicants' disclosure meets the written description standard with respect to the presently claimed invention.

For at least the reasons discussed above, when viewed in light of the factors articulated in *Capon v. Eshhar*, it is clear that Applicants' disclosure meets the written description requirement with respect to human antibodies that bind to dendritic cells comprising the presently claimed heavy and light chain variable region sequences. Indeed, the enclosed supporting prior art publications even establish that one of ordinary skill in the art had possession of antibodies having the same binding specificity based on a common CDR3 sequence alone. Clearly, this is also holds true for antibodies defined by full length variable region sequences. The prior art also clearly established that a broad variety of human framework regions were well known that could be used with such CDR and variable region sequences. Thus, when viewed in light of the extensive knowledge in the field, maturity of the science and predictability of generating human antibodies at the time of the present invention, claim 80 clearly meets the written description requirement.

(C) Original Claim 81

The Examiner asserts that the germline designations of original claim 81 are not disclosed in the specification. Applicants respectfully traverse this rejection. However to expedite prosecution, claim 81 has been canceled. Therefore, this rejection is moot.

Original Claims 82-86 and 88

With regard to the limitations of original dependent claims, the Examiner states these limitations are not stated "in the context of the B11 antibody of SEQ ID NOs:2 and 4."

Applicants respectfully traverse this rejection. However, to expedite prosecution, the presently claimed human antibodies (or antigen binding portions) include the heavy and light variable chain CDR3 regions (or conservative sequence modifications thereof), *i.e.*, the CDR3 regions of SEQ DI NOs: 2 and 4 (*i.e.*, of the B11 antibody). Accordingly, the rejection is now moot.

The Examiner further states that "no affinity of at least about 10^8 M^{-1} is disclosed and there is no disclosure of an antibody which dissociates from DCs with a rate of $10^{-3}S^{-1}$ or less."

Applicants disagree and respectfully point the Examiner to, for example, page 3, lines 7-8, of the present specification which explicitly describes antibodies having an affinity constant of "at least 10^8 M^{-1}" and page 3, lines 11-12, which explicitly describes antibodies having a dissociation constant (K_{dis}) of 10^{-3} s^{-1} or less, preferably about 10^{-4} s^{-1}, more preferably, 10^{-5} s^{-1}, and most preferably, 10^{-6} s^{-1}.

(I) Original Claim 87

According to the Examiner, only the B11 antibody is described as binding to the human macrophage mannose receptor comprising the amino acid sequence shown in SEQ ID NO:7 and not "an antibody with a specific V light and V heavy portion but any constant portions."

Applicants respectfully traverse and refer to their arguments above. Based at least on the foregoing, the claimed antibodies which include the heavy and light variable chain regions of SEQ ID NOs:2 and 4 joined to constant regions other than the constant regions of the B11 antibody are fully described and enabled by the present specification.

(K) Original Claim 90

The subject matter of original claim 90 is not encompassed by the pending claims. Therefore, this rejection is moot.

Rejection of Original Claims 81-91 Under 35 U.S.C. §112, First Paragraph

Original claim 81 and original dependent claims 82-91 (to the extent that they depend from claim 81) are rejected as not being sufficiently described under 35 U.S.C. §112, first paragraph. According to the Examiner, "[t]here is insufficient written description to show that Applicant was in possession of an isolated human monoclonal antibody comprising the product of the human germline V_H5-51 gene and human germline V_KL15 gene."

Applicants respectfully traverse this rejection. However, to expedite prosecution, the pending claims do not encompass the subject matter of original claim 81. Therefore this rejection is moot.

SUMMARY

In view of the foregoing amendments and arguments, reconsideration and withdrawal of all the rejections, and allowance of this application with all pending claims are respectfully requested. If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call (617) 227-7400.

Applicants believe no additional fee is due with this response. However, if an additional fee is due, please charge our Deposit Account No. 12-0080, under Order No. MXI-166 from which the undersigned is authorized to draw.

Dated: 23 Jan. 06

Respectfully submitted,

By _____
Jeanne M. DiGiorgio
Registration No: 41,710
LAHIVE & COCKFIELD, LLP
28 State Street
Boston, Massachusetts 02109
(617) 227-7400
(617) 742-4214 (Fax)
Attorney For Applicants